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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 19

Application Number: 08/540,343
Filing Date: October 6, 1995
Appellant(s): Hallahan et al.

Steven L. Highlander
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed March 5, 1998.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on March 5, 1998 has been entered. However it is noted that the amendment to claim 38 contains a typographical error. As recited in line 1, "tumor the cell" should be --the tumor cell--. It is presumed that this error will be rectified.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the groups of claims 15 and 24, claims 51-53, claims 10, 11, 21, 27, 36, 37, 44 and 45, and claims 25 and 47 do not stand or fall together, presumably each group with each other and claims on appeal not cited, and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Art of Record

The following is a listing of the art of record relied upon in the rejection of claims under appeal.

Orkin, S.H., et al. "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy", issued December 7, 1995 by the U.S. National Institutes of Health (38 pages).

Lafont, A., et al. "Which gene for restenosis?" Lancet, vol. 346 (Dec. 2, 1995), pp. 1442-1443.

Marshall, E. "Gene therapy's growing pains." Science, vol. 269 (Aug. 25, 1995), pp. 1050-1055.

Culver, K.W., et al. "Gene therapy for cancer." Trends Genet., vol. 10, no. 5 (May 1994), pp. 174-178.

Hodgson, C.P. "Advances in vector systems for gene therapy." Exp. Opin. Ther. Patents, vol. 5, no. 5 (1995), pp. 459-468.

Miller, N., et al. "Targeted vectors for gene therapy." FASEB J., vol. 9, no. 2 (Feb. 1995), pp. 190-199.

Dorudi, S., et al. "Gene transfer therapy in cancer." Brit. J. Surg., vol. 80 (1993), pp. 1442-1443.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 8, 10, 11, 13, 15, 18-27 and 35-55 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 8, 10, 11, 13, 15, 18-24 and 25-27 are broadly drawn to methods of inhibiting tumor growth *in vivo* or enhancing radiation treatment of a tumor *in vivo*, or are drawn to methods of killing tumor cells, implicitly either *in vivo* or *in vitro*, by administration of a herpes simplex virus (HSV), which encompass HSV comprising a heterologous gene, in combination with a dose of ionizing radiation. It is noted that HSV encompasses only two known herpesviruses, HSV-1 and HSV-2. Some claims limit the tumor cell type, i.e. human brain or breast tumor, which is still a generic tumor cell derived from either breast or brain (claims 10, 11, 21 and 27); limit the HSV virus to HSV-1 (claims 15 and 24); or limit the

route of administration of the HSV, oral or intravenous (claim 20). None of these claims limits the specific tumor type. Claims 35-55 are broadly drawn to methods of inhibiting tumor growth *in vivo* or enhancing radiation treatment of a tumor *in vivo*, or are drawn to methods of killing tumor cells, implicitly either *in vivo* or *in vitro*, by administration of an unspecified adenovirus, which does not comprise a heterologous gene, in combination with a dose of ionizing radiation. Some claims limit the tumor cell type to brain or breast tumor cells (claims 36, 37, 44 and 49; limit the adenovirus to Ad5, a human adenovirus (claims 51-53); or limit the route of administration of the adenovirus, intravenous (claim 54) or injection into the tumor site (claim 47). Except for claim 47, none of the claims recite the preferred mode of viral delivery to tumor cells which was direct intralesional injection into the tumor (see specification, for example, page 11, lines 8-10). In general, the claims broadly encompass killing of any tumor, regardless of specific cell type; recitation that tumor cells are brain or breast tumor cells, encompasses a variety of different tumor cell types originating from brain or breast tissue. In addition, most claims encompass any mode of administration; any animal (or mammal) carrying the tumor; and any HSV, both lacking and comprising heterologous, therapeutic genes, or adenovirus. None of the claims bring all of the specific limitations into a single claim. As disclosed on page 4, lines 15-16 and page 12, lines 7-8, the invention is directed to increasing the effectiveness of radiation therapy for treating tumors, i.e. cancer, by the administration of HSV or adenovirus in conjunction with radiation therapy. Whether the claimed invention is enabled by the specification must be viewed in this light. Therefore, the

claims are either explicitly or implicitly, in light of the specification, limited to methods for enhancing killing of tumor cells by radiation therapy alone by co-administration of the HSV or adenoviruses in anti-tumor therapy.

The specification presents working examples involving a tumor model system in which cells of human tumor cell lines are implanted subcutaneously into a mouse hindlimbs of nude mice, i.e. naive, immune compromised mice, to form tumor xenografts. Specifically, in the first example, human glioblastoma cells were implanted and crippled HSV-1 were injected at an unspecified location, and in the second example, human colon carcinoma cells were implanted and Ad5 was injected into the xenografts. It must be emphasized that human viruses have been used to infect human cells implanted in an immune compromised mouse. From these single examples it cannot be predicted whether HSV or Ad5 could be used in treating spontaneous tumors in any animal, except perhaps humans; that any adenovirus that naturally infects one animal, e.g. human as with Ad5, could be used to treat tumors in a different animal; and whether the treatment would work as expected in an immune competent animal. The question of whether the model system featured in the working examples is predictive of treating spontaneous tumors that arose *de novo* from an animal's own cells is further addressed below.

The specification provides minimal guidance for carrying out the invention either with HSV or with adenovirus. Modes of viral administration (see page 11, lines 5-11) and therapeutic viral doses (see page 9, lines 17-20) are described in sweeping terms without

correlating dose to the modes of administration or tumor size. As mentioned above, the preferred mode of viral administration is direct intralesional injection. Clearly, the dose used for this mode of administration would be wholly inadequate for systemic modes of administration like intravenous and oral administration. There is no guidance concerning specific tumor types that can be treated with the claimed methods; rather the specification implies that all tumor types are treatable. The specification does not disclose how the working examples using the model system are to be extrapolated to treatment of tumors as claimed.

The prior art does not disclose the combination viral and radiation therapy claimed. Prior art on using adenovirus in tumor treatment was limited to adenoviral vectors carrying therapeutic transgenes; such adenovirus are specifically excluded from claims 35-55. The specification discusses preliminary results for the use of certain crippled HSV-1 strains in killing tumor cells (page 3, lines 7-25; page 19, lines 5-19). It is not clear that the mouse model used in the specification would be considered correlatable to the results that the skilled artisan would observe upon practicing the invention in any and all animals, including humans on spontaneous tumors. The model system presented in the specification involves the implantation of foreign cells into a nude mouse, which is naive and immune compromised, to induce the formation of an artificial tumor comprising the foreign cells. There is no evidence of record, either in the specification or prior art, to show that results obtained with this model system can be correlated to spontaneous tumor formation from cells of the animal. Orkin et al. reviews the state of the art of gene therapy up to shortly after the instant invention was filed.

Although, Orkin et al. deals primarily with the unpredictability of gene therapy, several statements made therein are generally applicable to the use of model systems for cancer treatment. In point 5 (page 1-2), Orkin et al. states that:

> "Although animal investigations are often valuable, it is not always possible to extrapolate directly from animal experiments to human studies. Indeed, in some cases, such as cystic fibrosis, cancer, and AIDS, animal models do not satisfactorily mimic the major manifestations of the corresponding human disease"

On page 11, second and third paragraphs, Orkin et al. emphasize the importance of relevant animal models, and state that many "mouse models often do not faithfully mimic the relevant human conditions". Orkin et al. also indicate that when dealing with cancer, the relevance of animal models appears to be less predictive than with other single- gene disorders. On page 14 (second bullet), Orkin et al. state that animal models are not satisfactory for studying human disorders such as cancer, and that human studies are therefore necessary to develop effective treatments for cancer and other diseases. Also, Lafont et al. disclose at page 1442, paragraph bridging columns 1 and 2:

> "The tumoral concept is attractive because it might explain the clinical picture, proposes a target (smooth-muscle-cell proliferation), is supported by animal models, and paves the way to treatment strategy (genes to inhibit smooth-muscle cell proliferation). The main drawback is related to the discrepancy between striking successes in various animal models and the general failure in human beings."

Finally, Culver et al., a review of cancer gene therapy, briefly discusses the inadequacies of a rat model for treatment of brain tumors in humans, and laments that a more suitable model is not available (page 177, col. 1, full para. 1).

Claims 8, 10, 11, 13, 15 and 18-27 also encompass embodiments of the methods using HSV vectors comprising heterologous genes expressing therapeutic products that are detrimental to tumor cells, e.g. tumor necrosis factor, cytokines, etc., which is a form of gene therapy (see specification page 6, para. 1). The only such therapeutic product specifically described is tumor necrosis factor α (TNFα), and the working examples include an HSV-1 vector encoding TNFα. At the time the invention was made it was not clear that transfer of any exogenous therapeutic gene could be effectively accomplished without having to undertake undue experimentation. This point is clearly supported by the art, described in the succeeding paragraphs, which recognizes the infancy of gene therapy and the tremendous amount of experimentation still required in the art.

Marshall et al. states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col. 3). James Wilson, one highly skilled in the art, is quoted in Marshall et al. saying that " '{t}he actual vectors - how we're going to practice our trade - haven't been discovered yet" (p. 1055, col. 2).

Culver et al., reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge" (p. 178).

Hodgson discusses the drawbacks of viral transduction and chemical transfection methods, and states that " {d}eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pp. 459-460).

Miller et al. also review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col.1). Therefore even if the claimed method could inhibit the growth of tumor cells *in vivo*, it would require further experimentation to develop a suitable system for delivery of the gene construct.

Moreover, regarding genetically engineered HSV vectors comprising cytokines for inhibiting tumor cell growth, Dorudi et al. state at page 569, column 1, first paragraph:

> "Although cytokine gene transfer offers an attractive approach to cancer vaccination, its use must be based on a clear understanding of both the tumor type and the immune response

> that the patient is able to mount against it. This may vary even between patients with the same tumor and obviously limits clinical adoption of this strategy. Finally, the choice of therapy should also be guided by the growth requirements of the tumor, as the local production of certain cytokines can lead to enhanced growth of some tumors through an autocrine mechanism. Thus the delivery of an inappropriate cytokine to tumor cells may actually promote aggressive cell growth. Work is under way to rationalize the use of cytokine gene transduction of tumor cells to produce optimal stimulation of tumor-infiltrating effector cells."

Therefore, even if it were possible at some time to achieve sufficient cytokine gene transfer to any and all tumors, the outcome would clearly be unpredictable as is evidenced by those of skill in the art.

In view of the breadth of the claims, the lack of substantive guidance in the specification regarding the specifics of the embodiments encompassed in the broad scope, the lack of relevant working examples, and the unpredictability of the subject matter being claimed, it is concluded that undue experimentation would be required to practice the invention as it is now claimed.

(11) Response to Argument

It is argued that the rejection is maintained because the claims are not restricted to HSV-1 and Ad5 because of the breadth of treatment of any and all tumor types in any and all

animals. The point that HSV-2 would be expected to behave as HSV-1, exemplified, and the point that any human adenovirus ("the other 41 serotypes" referred to in the brief at page 7, line 2) would behave as did exemplified Ad5 are conceded, at least in the context of the model system employed in the specification. As mentioned above, the predictability of the model system is at issue, as is the predictability of using any adenovirus or HSV-1 to infect tumor cells of any animal, or more specifically to provide any contribution to killing tumor cells by radiation. According to the specification (page 4, lines 15-16), the invention is to increase the cytotoxic effect of radiation therapy of tumors. The question of whether the specification enables the claimed invention must be evaluated in that context.

On the second point raised in the brief (bottom of page 7), recitation of breast or brain tumors does not actually limit the claims to cell type, but to tumor location. It is acknowledged that HSV and Ad5 are able to infect a wide variety of cell types *in vitro* and presumably when cultured cells are implanted in a foreign, immune-compromised host. Whether, these viruses would be able to infect cells of any type of spontaneous tumor in an immune competent animal, e.g. human, is another question. As presented above, the prior art recognized the problems inherent in extrapolation from results obtained with animal models to cancer treatment in humans, and therein lies a significant source of unpredictability with respect to the

claimed invention and instant specification *inter alia* as regards treatment of any and all tumor types.

On the third and final point raised in the brief (full para. 2, page 8), it is argued that the claims recite that the virus reaches its target. Whether the functional limitation in the claim is present or absent is not the issue, but whether the specification discloses how that function will be accomplished and whether sufficient virus will reach the tumor to have any effect. This then depends on the guidance in the specification regarding dose in the context of mode of administration of virus; as indicated above, the specification provides no such guidance. It is further argued that those of skill in the art could determine "the precise mode of administration that best exploits the present invention". However, this is an invitation to experimentation in order to provide the necessary information that is lacking in the specification, since it is unclear whether this same skilled artisan would be able to predict *a priori* whether a suitable route of administration and dose of virus would be effective for a given tumor in a given location. Appellants do not point to any guidance in the specification that would allow one skilled in the art to make such an *a priori* prediction. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> "that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical

reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

While the results using the model system disclosed in the specification are promising, the minimal guidance in the specification and the unpredictability of the model system and in the art of cancer treatment shows that undue experimentation would be required to turn the promise into therapeutic practice.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

SDP

Scott D. Priebe, PhD.
Patent Examiner
April 8, 1998

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